Remarks

The Interview

Applicants and the undersigned greatly appreciate the examiner taking the time (particularly at such an early hour) to speak to them, and to discuss not only the invention - the use of orally administered arsenic trioxide which is interestingly as efficacious as intravenous arsenic trioxide but much safer. The undersigned believes that the claims as amended reflect the understanding of the parties as to the novel and unexpected properties of this formulation and methods of orally administering arsenic trioxide. The enclosed Declaration more clearly demonstrates how the peak plasma levels are different for intravenous versus oral administration (i.e., area under the curve is the same, but the peak is lower with oral administration), and as a result the cardiotoxicity in the form of cardiac arrhythmias, which is positively correlated with the peak plasma arsenic level rather than the total amount entering the body, is significantly less after oral administration than with intravenous administration.

For clarification, it should be noted that the AUCs (bioavailability) in plasma after intravenous administration and oral dosing pertain to patient 1, whose AUC details were published in Table 2 of Kumana, et al., Eur. J. Clin. Pharmacol. 58, 521-526 (2002) (copy enclosed).

Amended Claims

Claims 1 and 9 have been amended to be specific to dosage forms suitable for oral administration but not intravenous administration, by incorporating the dosage forms of claim 10 into claim 1. Claims 4 and 10 have been cancelled.

Method claim 28 has been amended to recite that the orally administered arsenic trioxide does not produce the cardiotoxicity (in the form of cardiac arrhythmias) of intravenous administration. This is demonstrated by example 2 in the application, as was discussed during the interview. See paragraph 107 of the published application. This is also clearly demonstrated by the clinical data presented in the accompanying Second Declaration under 37 C.F.R. 1.132.

New method claim 45 parallels the language of original claim 10, now incorporated into amended claim 1.

Rejections Under 35 U.S.C. § 102 and 103

Claims 1-3 and 7 were rejected under 35 U.S.C. § 102(b) as anticipated by, or under 103 as obvious over WO 99/24029. Claims 1-3, 7 and 8 were rejected under 35 U.S.C. § 102(a) as anticipated by CN1370540. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

As discussed at the interview, the prior art does not disclose a formulation for oral rather than intravenous administration. The prior art does not recognize that one can achieve the same bioavailability with oral administration as with intravenous (indeed, contrary to what is obtained

with most drugs) yet have lower peak concentrations and thereby avoid the very serious side effect of cardiotoxicity in the form of cardiac arrhythmias, which can result in death of patients.

Rejections Under 35 U.S.C. § 103

Claims 1-42 were rejected under 35 U.S.C. § 103(a) as obvious over WO 99/24029 and CN1370540. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The prior art does not recognize that arsenic trioxide can be orally administered in an effective amount with reduced side effects, particularly cardiac arrhythmias, as compared to i.v. administration, and therefore that the formulation as well as method of administration are both different as well as non-obvious. As the inventors explained and as demonstrated by the submitted declarations, a lower dose with equal efficacy as compared to i.v. administration can be obtained using oral administration. One cannot just directly compare total dosage in this regard, but must look at the amount per kg of patient weight. The formulations as defined by the amended claims are now limited to formulations suitable only for oral administration, not intravenous administration.

Indeed, CN137540 does not even mention oral administration of the drug, only conventional treatment of leukemia with arsenic trioxide.

WO 99/24029 at page 17 states that arsenic trioxide can be administered orally or topically or parenterally. Topical administration is clearly impossible. Similarly, the boiler plate on page 16 provides that one could administer drug by inhalation, another impossibility. There

is no disclosure of how much drug is given orally nor in what form it is given, other than to provide an 8-fold range of 2.5 to 40 mg. The dosage for intravenous treatment is stated to be greater than or less than 10 mg/day, with a preferred dose of 0.1 to about 5 mg/KG/day (page 17, lines 35-37).

WO 99/24029 fails to teach one skilled in the art to actually administer the formulation orally. It is well known in the art that bioavailability is generally considerably less orally than by intravenous administration. Moreover, it is common with administration of chemotherapeutic drugs to cause an extremely painful condition called mucositis, an inflammation of the mucosa. For these two reasons alone, one would not expect to be able to orally administer an effective dose, but with fewer side effects, in particular, cardiotoxicity in the form of cardiac arrhythmias. When administered orally rather than intravenously, one would expect to need a much larger dosage, not a lower dosage. There is no such teaching in WO 99/24029. ALL of the examples demonstrate intravenous administration and in the United States the drug is approved only for intravenous administration. Since oral administration is cheaper, easier, and safer, there is no question but that if those skilled in the art had believed such an option was available, they would have demonstrated its use. This is even more so considering the very dangerous side effects associated with intravenous administration (*see* package insert submitted June 6, 2007) which are avoided by oral administration, as demonstrated by the evidence that applicants have submitted. *See, for example,* Blood, 98(5), 1632-1634 (1 September 2001) (submitted June 6, 2007).

Applicants provide pharmacokinetic differences that show that contrary to expectation, the arsenic trioxide formulation is orally bioavailable at substantially the same amount as the intravenously administered drug. This was even more surprising given the very low solubility and pH dependence of the arsenic trioxide in water.

In summary, the prior art neither discloses the compositions and methods as presently claimed, nor do they make obvious, in view of the differences in dosages, effective amounts, and lower cardiotoxicity in the form of cardiac arrhythmias, which could not have been predicted and were in fact taught away from by the prior art.

Allowance of claims 1-3, 5, 6, 9, 28-34, and 38-45 is respectfully solicited.

Respectfully submitted,

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